

## 結語

本研究では、成体脳神経系前駆細胞と既存神経回路網との機能的関わりについての解析を行った。海馬および大脳皮質において、分裂能を有するネスチン陽性神経系前駆細胞は共に興奮性 GABA 入力を受け取っており、神経回路の活動に伴いダイナミックな応答を示すことが初めて示された。分裂能を持った神経系前駆細胞がシナプス性の入力を受け取っていたことは非常に驚くべき結果である。また、通常成体脳内において抑制性の神経伝達物質であると考えられてきた GABA がこれらの前駆細胞には興奮性に作用することも、非常に興味深い結果である。この興奮性 GABA 入力は、神経系前駆細胞のニューロン分化や神経栄養因子（BDNF）の放出を促す極めて重要な因子であることが結論付けられ、この性質が神経回路網へ可塑性をもたらしていると考えられる。また最近、他の領域においても神経系前駆細胞は分化段階初期において興奮性 GABA 入力を受け取っていることを示す結果が相次いで報告され、神経系前駆細胞の分化や機能発現への興奮性 GABA 入力の関与は共通した現象であると考えられる。また成体脳内における情報伝達システムはニューロン間だけではなく、神経系前駆細胞もまたシナプスを形成し、脳回路の機能に関わっていると考えられ、神経回路の活動に依存した脳の可塑性を理解する上で重要な知見が得られたと言えよう。そして大人になってからでも、脳の活動を高めることで、いつまでも柔軟性に富んだ脳を保つことができるのではないかと期待できる。

## 参考文献

- Abrous, D.N., Koehl, M., and Le Moal, M. (2005). Adult neurogenesis : from precursors to network and physiology. *Physiol. Rev.* 85, 523-569.
- Alsina, B., Vu, T., and Cohen-Cory, S. (2001). Visualizing synapse formation in arborizing optic axons in vivo: dynamics and modulations by BDNF. *Nat. Neurosci.* 4, 1093-1101.
- Altman, J., and Das, G.D. (1965). Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J. Comp. Neurol.* 124, 319-335.
- Ando, S., Kobayashi, S., Waki, H., Kon, K., Fukui, F., Tadanuma, T., Iwamoto, M., Takeda, Y., Izumiya,a, N., Watanabe, K., Nakamura, H. (2002). Animal model of dementia induced by entorhinal synaptic damage and partial restoration of cognitive deficits by BDNF and carnitin. *J. Neurosci. Res.* 70, 519-527.
- Antonopoulos, J., Pappas, I.S., and Parnavelas, J.G. (1997). Activation of GABA<sub>A</sub> receptor inhibits the proliferative effects of bFGF in cortical progenitor cells. *Eur. J. Neurosci.* 9, 291-298.
- Bagnard, D., Lohrum, M., Uziel, D., Puschel, A.W., and Bolz, J. (1998). Semaphorins act as attractive and repulsive guidance signals during the development of cortical projections. *Development* 125, 5043-5053.

Bao, S., Chan, V.T., and Merzenich, M.M. (2001). Cortical remodelling induced by activity of ventral tegmental dopamine neurons. *Nature* 412, 79-83.

Barakat, L., Wang, D., and Borday, A. (2002). Carrier-mediated uptake and release of taurine from Bergmann glia in rat cerebellar slices. *J. Physiol.* 541, 753-767.

Barde, Y.A., Edgar, D., and Thoenen, H. (1982). Purification of a new neurotrophic factor from mammalian brain. *EMBO J.* 1, 549-553.

Bartos, M., Vida, I., Frotscher, M., Meyer, A., Monyer, H., Geiger, J.R., and Jonas, P. (2002). Fast synaptic inhibition promotes synchronized gamma oscillations in hippocampal interneuron networks. *Proc. Natl. Acad. Sci. USA* 99, 13222-13227.

Ben-Ari, Y. (2002). Excitatory actions of GABA during development: the nature of the nurture. *Nat. Rev. Neurosci.* 3, 728-739.

Bengzon, J., Kokaia, Z., Elmer, E., Nanobashvili, A., Kokaia, M., and Lindvall, O. (1997). Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. *Proc. Natl. Acad. Sci. USA* 94, 10432-10437.

Bergles, D.E., Roberts, J.D., Somogyi, P., and Jahr, C.E. (2000). Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. *Nature*

405, 187-191.

Blümcke, I., Schewe, J.C., Normann, S., Brustle, O., Schramm, J., Elger, C.E., and Wiestler, O.D. (2001). Increase of nestin-immunoreactive neural precursor cells in the dentate gyrus of pediatric patients with early-onset temporal lobe epilepsy. *Hippocampus* 11, 311-321.

Bragin, A., Jando, G., Nadasdy, Z., Hetke, J., Wise, K., and Buzsaki, G. (1995). Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. *J. Neurosci.* 15, 47-60.

Bu, J., Banki, A., Wu, Q., and Nishiyama, A. (2004). Increased NG2(+) glial cell proliferation and oligodendrocyte generation in the hypomyelinating mutant shiverer. *Glia* 48, 51-63.

Buffo, A., Vosko, M.R., Ertürk, D., Hamann, G.F., Jucker, M., Rowitch, D., Götz, M. (2005). Expression pattern of the transcription factor Olig2 in response to brain injuries: Implications for neuronal repair. *Proc. Natl. Acad. Sci. USA* 102, 18183-18188.

Burbach, G.J., Hellweg, R., Haas, C.A., Del Turco, D., Deicke, U., Abramowski, D., Jucker, M., Staufenbiel, M., and Deller, T. (2004). Induction of brain-derived neurotrophic factor in plaque-associated glial cells of aged APP23 transgenic mice. *J. Neurosci.* 24, 2421-2430.

Buzsaki, G. (2002). Theta oscillations in the hippocampus. *Neuron* 33, 325-340.

Calford, M.B., and Tweedale, R. (1988). Immediate and chronic changes in responses of somatosensory cortex in adult flying-fox after digit amputation. *Nature* 332, 446-448.

Calford, M.B., and Tweedale, R. (1990). Interhemispheric transfer of plasticity in the cerebral cortex. *Science* 249, 805-807.

Calford, M.B., and Tweedale, R. (1991). C-fibres provide a source of masking inhibition to primary somatosensory cortex. *Proc. Biol. Sci.* 243, 269-275.

Cameron, H.A., Woolley, C.S., McEwen, B.S., and Gould, E. (1993). Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. *Neurosci.* 56, 337-344.

Cameron, H.A., McEwen, B.S., and Gould, E. (1995). Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. *J. Neurosci.* 15, 4687-4692.

Carleton, A., Petreanu, L.T., Lansford, R., Alvarez-Buylla, A., and Lledo, P.M. (2003). Becoming a new neuron in the adult olfactory bulb. *Nat. Neurosci.* 6, 507-518.

Castren, E., Zafra, F., Thoenen, H., and Lindholm, D. (1992). Light regulates expression of brain-derived neurotrophic factor mRNA in rat visual cortex. Proc. Natl. Acad. Sci. USA. 89, 9444-9448.

Cellerino, A., Maffei, L., and Domenici, L. (1996). The distribution of brain-derived neurotrophic factor and its receptor trkB in parvalbumin-containing neurons of the rat visual cortex. Eur. J. Neurosci. 8, 1190-1197.

Chittajallu, R., Aguirre, A., and Gallo, V. (2004). NG2-positive cells in the mouse white and grey matter display distinct physiological properties. J. Physiol. 561, 109-122.

Chklovskii, D.B., Mel, B.W., and Svoboda, K. (2004). Cortical rewiring and information storage. Nature 431, 782-788.

Chrobak, J.J., and Buzsaki, G. (1998). Gamma oscillations in the entorhinal cortex of the freely behaving rat. J. Neurosci. 18, 388-398.

Csicsvari, J., Jamieson, B., Wise, K.D., and Buzsaki, G. (2003). Mechanisms of gamma oscillations in the hippocampus of the behaving rat. Neuron 37, 311-322.

Dai, X., Lercher, L.D., Clinton, P.M., Du, Y., Livingston, D.L., Vieira, C., Yang, L., Shen, M.M., and Dreyfus, C.F. (2003). The trophic role of oligodendrocytes in the

basal forebrain. *J. Neurosci.* 23, 5846-5853.

Deisseroth, K., Singla, S., Toda, H., Monje, M., Palmer, T.D., and Malenka, R.C. (2004). Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron* 42, 535-552.

de Lanerolle, N.C., Kim, J.H., Robbins, R.J., and Spencer, D.D. (1989). Hippocampal interneuron loss and plasticity in human temporal lobe epilepsy. *Brain Res.* 495, 387-395.

Demarque, M., Represa, A., Becq, H., Khalilov, I., Ben-Ari, Y., and Aniksztejn, L. (2002). Paracrine intercellular communication by a Ca<sup>2+</sup>- and SNARE-independent release of GABA and glutamate prior to synapse formation. *Neuron* 36, 1051-1061.

De Paola, V., Holtmaat, A., Knott, G., Song, S., Wilbrecht, L., Caroni, P., and Svoboda, K. (2006). Cell type-specific structural plasticity of axonal branches and boutons in the adult neocortex. *Neuron* 49, 861-875.

Diamond, M.E., Armstrong-James, M., and Ebner, F.F. (1993). Experience-dependent plasticity in adult rat barrel cortex. *Proc. Natl. Acad. Sci. U S A.* 90, 2082-2086.

Dobrossy, M.D., Drapeau, E., Aurousseau, C., Le Moal, M., Piazza, P.V., and

Abrous, D.N. (2003). Differential effects of learning on neurogenesis: learning increases or decreases the number of newly born cells depending on their birth date. *Mol. Psychiatry* 8, 974-982.

Drapeau, E., Mayo, W., Aurousseau, C., Le Moal, M., Piazza, P.V., and Abrous, D.N. (2003). Spatial memory performances of aged rats in the water maze predict levels of hippocampal neurogenesis. *Proc. Natl. Acad. Sci. U S A* 100, 14385-14390.

Durand, B., Gao, F.B., and Raff, M. (1997). Accumulation of the cyclin-dependent kinase inhibitor p27/Kip1 and the timing of oligodendrocyte differentiation. *EMBO J.* 16, 306-317.

Elmariah, S.B., Crumling, M.A., Parsons, T.D., and Balice-Gordon, R.J. (2004). Postsynaptic TrkB-mediated signaling modulates excitatory and inhibitory neurotransmitter receptor clustering at hippocampal synapses. *J. Neurosci.* 24, 2380-2393.

Eriksson, P.S., Perfilieva, E., Björk-Eriksson, T., Alborn, A.M., Nordborg, C., Peterson, D.A., and Gage, F.H. (1998). Neurogenesis in the adult human hippocampus. *Nat. Med.* 4, 1313-1317.

Ernfors, P., Ibanez, C.F., Ebendal, T., Olson, L., and Persson, H. (1990). Molecular cloning and neurotrophic activities of a protein with structure similarities to nerve growth factor: developmental and topographical expression in the brain.

Proc. Natl. Acad. Sci. U S A. 87, 5454-5458.

Ernfors, P., Bengzon, J., Kokaia, Z., Persson, H., and Lindvall, O. (1991). Increased levels of messenger RNAs for neurotrophic factors in the brain during kindling epileptogenesis. *Neuron* 7, 165-176.

Essrich, C., Lorez, M., Benson, J.A., Fritschy, J.M., and Lüscher, B. (1998). Postsynaptic clustering of major GABA<sub>A</sub> receptor subtypes requires the gamma 2 subunit and gephyrin. *Nat. Neurosci.* 1, 563-571.

Espósito, M.S., Piatti, V.C., Laplagne, D.A., Morgenstern, N.A., Ferrari, C.C., Pitossi, F.J., and Schinder, A.F. (2005). Neuronal differentiation in the adult hippocampus recapitulates embryonic development. *J. Neurosci.* 25, 10074-10086.

Fagiolini, M., Fritschy, J.M., Low, K., Mohler, H., Rudolph, U., and Hensch, T.K. (2004). Specific GABA<sub>A</sub> circuits for visual cortical plasticity. *Science* 303, 1681-1683.

Fellous, J.M., and Sejnowski, T.J. (2000). Cholinergic induction of oscillations in the hippocampal slice in the slow (0.5-2 Hz), theta (5-12 Hz), and gamma (35-70 Hz) bands. *Hippocampus* 10, 187-197.

Feng, R., Rampon, C., Tang, Y.P., Shrom, D., Jin, J., Kyin, M., Sopher, B., Miller, M.W., Ware, C.B., Martin, G.M., Kim, S.H., Langdon, R.B., Sisodia, S.S., and

Tsien, J.Z. (2001). Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. *Neuron* 32, 911-926.

Ferrer, I., Krupinski, J., Goutan, E., Marti, E., Ambrosio, S., and Arenas E. (2001). Brain-derived neurotrophic factor reduces cortical cell death by ischemia after middle cerebral artery occlusion in the rat. *Acta Neuropathol.* 101, 229-238.

Feustel, P.J., Jin, Y., and Kimelberg, H.K. (2004). Volume-regulated anion channels are the predominant contributors to release of excitatory amino acids in the ischemic cortical penumbra. *Stroke* 35, 1164-1168.

Filippov, V., Kronenberg, G., Pivneva, T., Reuter, K., Steiner, B., Wang, L.P., Yamaguchi, M., Kettenmann, H., and Kempermann, G. (2003). Subpopulation of nestin-expressing progenitor cells in the adult murine hippocampus shows electrophysiological and morphological characteristics of astrocytes. *Mol. Cell. Neurosci.* 23, 373-82.

Fisahn, A., Pike, F.G., Buhl, E.H., and Paulsen, O. (1998). Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro. *Nature* 394, 186-189.

Freund, T.F., and Buzsaki, G. (1996). Interneurons of the hippocampus. *Hippocampus* 6, 347-470.

Fujioka, T., Fujioka, A., and Duman, R.S. (2004). Activation of cAMP signaling facilitates the morphological maturation of newborn neurons in adult hippocampus. *J. Neurosci.* 24, 319-328.

Fukuda, S., Kato, F., Tozuka, Y., Miyamoto, Y., and Hisatsune, T. (2003). Two distinct subpopulations of nestin-positive cells in adult mouse dentate gyrus. *J. Neurosci.* 23, 9357-9366.

Fusco, M., Vantini, G., Schiavo, N., Zanotti, A., Zanoni, R., Facci, L., and Skaper, S.D. (1993). Gangliosides and neurotrophic factors in neurodegenerative diseases: from experimental findings to clinical perspectives. *Ann. N. Y. Acad. Sci.* 695, 314-317.

Galarreta, M., and Hestrin, S. (2002). Electrical and chemical synapses among parvalbumin fast-spiking GABAergic interneurons in adult mouse neocortex. *Proc. Natl. Acad. Sci. U S A.* 99, 12438-12443.

Ge, S., Goh, E.L., Sailor K.A., Kitabatake, Y., Ming, G.L., and Song, H. (2005). GABA regulates synaptic integration of newly generated neurons in the adult brain. *Nature* 439, 589-593.

Ge, W.P., Yang, X.J., Zhang, Z., Wang, H.K., Shen, W., Deng, Q.D., and Duan, S. (2006). Long-term potentiation of neuron-glia synapses mediated by Ca<sup>2+</sup>-permeable AMPA receptors. *Science* 312, 1533-1537.

Ghosh, A., Carnahan, J., and Greenberg, M.E. (1994). Requirement for BDNF in activity-dependent survival of cortical neurons. *Science* 263, 1618-1623.

Gonthier, B., Nasarre, C., Roth, L., Perraut, M., Thomasset, N., Roussel, G., Aunis, D., and Bagnard, D. (2006). Functional Interaction between Matrix Metalloproteinase-3 and Semaphorin-3C during Cortical Axonal Growth and Guidance. *Cereb. Cortex* (in press).

Gorba, T., and Wahle, P. (1999). Expression of trkB and trkC but not BDNF mRNA in neurochemically identified interneurons in rat visual cortex *in vivo* and in organotypic cultures. *Eur. J. Neurosci.* 11, 1179-1190.

Hayder, T.F., Wang, F., Schwartz, M.L., and Rakic, P. (2000). Differentiation modulation of proliferation in the neocortical ventricular and subventricular zones. *J. Neurosci.* 20, 5764-5774.

Hennou, S., Khalilov, I., Diabira, D., Ben-Ari, Y., and Gozlan, H. (2002). Early sequential formation of functional GABA<sub>A</sub> and glutamatergic synapses on CA1 interneurons of the rat foetal hippocampus. *Eur. J. Neurosci.* 16, 197-208.

Hensch, T.K., and Stryker, M.P. (2004). Columnar architecture sculpted by GABA circuits in developing cat visual cortex. *Science* 303, 1678-1681.

Hensch, T.K. (2005). Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* 6, 877-888.

Holtmaat, A., Wilbrecht, L., Knott, G.W., Welker, E., and Svoboda, K. (2006). Experience-dependent and cell-type-specific spine growth in the neocortex. *Nature* 441, 979-983.

Horner, P.J., Power, A.E., Kempermann, G., Kuhn, H.G., Palmer, T.D., Winkler, J., Thal, L.J., and Gage, F.H. (2000). Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. *J. Neurosci.* 20, 2218-2228.

Houser, C.R., and Esclapez, M. (1996). Vulnerability and plasticity of the GABA system in the pilocarpine model of spontaneous recurrent seizures. *Epilepsy Res.* 26, 207-218.

Huang, Z.J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M.F., Maffei, L., and Tonegawa, S. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell* 98, 739-755.

Hughes, P.E., Alexi, T., Walton, M., Williams, C.E., Dragunow, M., Clark, R.G., and Gluckman, P.D. (1999). Activity and injury-dependent expression of inducible transcription. *Prog. Neurobiol.* 57, 421-450.

Imura, T., Kanatani, S., Fukuda, S., Miyamoto, Y., and Hisatsune, T. (2005).

Layer-specific production of nitric oxide during cortical circuit formation in postnatal mouse brain. *Cereb. Cortex* 15, 332-340.

Jabs, R., Pivneva, T., Hüttmann, K., Wyczynski, A., Nolte, C., Kettenmann, H. and Steinhäuser, C. (2005). Synaptic transmission onto hippocampal glial cells with hGFAP promoter activity. *J. Cell Sci.* 118, 3791-3803.

Jin, K., Xie, L., Kim, S.H., Parmentier-Batteur, S., Sun, Y., Mao, X.O., Childs, J., and Greenberg, D.A. (2004). Defective adult neurogenesis in CB1 cannabinoid receptor knockout mice. *Mol. Pharmacol.* 66, 204-208.

Jurić, D.M., Miklič, S., and Čarman-Kržan, M. (2006). Monoaminergic neuronal activity up-regulates BDNF synthesis in cultured neonatal rat astrocytes. *Brain Res.* 1108, 54-62.

Kamada, M., Li, R.Y., Hashimoto, M., Kakuda, M., Okada, H., Koyanagi, Y., Ishizuka, T., and Yawo, H. (2004). Intrinsic and spontaneous neurogenesis in the postnatal slice culture of rat hippocampus. *Eur. J. Neurosci.* 20, 2499-2508.

Katona, I., Sperlagh, B., Sik, A., Kafalvi, A., Vizi, E.S., Mackie, K., and Freund, T.F. (1999). Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. *J. Neurosci.* 19, 4544-4558.

Kempermann, G., Kuhn, H.G., and Gage, F.H. (1997). More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386, 493-495.

Kempermann, G., Jessberger, S., Steiner, B., and Kronenberg, G. (2004). Milestones of neuronal development in the adult hippocampus. *Trends Neurosci.* 27, 447-452.

Khazipov, R., Esclapez, M., Caillard, O., Bernard, C., Khalilov, I., Tyzio, R., Hirsch, J., Dzhala, V., Berger, B., and Ben-Ari, Y. (2001). Early development of neuronal activity in the primate hippocampus in utero. *J. Neurosci.* 21, 9770-9781.

Kilgard, M.P., and Merzenich, M.M. (1998). Plasticity of temporal information processing in the primary auditory cortex. *Nat. Neurosci.* 1, 727-731.

Klausberger, T., Roberts, J.D., and Somogyi, P. (2002). Cell type- and input-specific differences in the number and subtypes of synaptic GABA(A) receptors in the hippocampus. *J. Neurosci.* 22, 2513-2521.

Knott, G.W., Quairiaux, C., Genoud, C., and Welker, E. (2002). Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. *Neuron* 34, 265-273.

Kobayashi, M., and Buckmaster, P.S. (2003). Reduced inhibition of dentate granule cells in a model of temporal lobe epilepsy. *J. Neurosci.* 23, 2440-2452.

Koketsu, D., Mikami, A., Miyamoto, Y., and Hisatsune, T. (2003). Nonrenewal of neurons in the cerebral neocortex of adult macaque monkeys. *J. Neurosci.* 23, 937-942.

Komitova, M., Perfilieva, E., Mattsson, B., Eriksson, P.S., and Johansson, B.B. (2006). Enriched environment after focal cortical ischemia enhances the generation of astroglia and NG2 positive polydendrocytes in adult rat neocortex. *Exp. Neurol.* 199, 113-121.

Kornack, D.R., and Rakic, P. (1999). Continuation of neurogenesis in the hippocampus of the adult macaque monkey. *Proc. Natl. Acad. Sci. USA* 96, 5768-5773.

Kornack, D.R., and Rakic, P. (2001). Cell proliferation without neurogenesis in adult primate neocortex. *Science* 294, 2127-2130.

Korte, M., Carroll, P., Wolf, E., Brem, G., Thoenen, H., and Bonhoeffer, T. (1995). Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. *Proc. Natl. Acad. Sci. U S A.* 92, 8856-8860.

Kronenberg, G., Reuter, K., Steiner, B., Brandt, M.D., Jessberger, S., Yamaguchi, M., and Kempermann, G. (2003). Subpopulations of proliferating cells of the adult hippocampus respond differently to physiologic neurogenic stimuli. *J. Comp. Neurol.* 467, 455-63.

Kumar, S.S., and Buckmaster, P.S. (2006). Hyperexcitability, interneurons, and loss of GABAergic synapses in entorhinal cortex in a model of temporal lobe epilepsy. *J. Neurosci.* 26, 4613-4623.

Lee, M.G., Chrobak, J.J., Sik, A., Wiley, R.G., and Buzsaki, G. (1994). Hippocampal theta activity following selective lesion of the septal cholinergic system. *Neurosci.* 62, 1033-1047.

Leventhal, A.G., Wang, Y., Pu, M., Zhou, Y., and Ma, Y. (2003). GABA and its agonists improved visual cortical function in senescent monkeys. *Science* 300, 812-815.

Lin, S.C., and Bergles, D.E. (2004). Synaptic signaling between GABAergic interneurons and oligodendrocyte precursor cells in the hippocampus. *Nat. Neurosci.* 7, 24-32.

Lin, S.C., Huck, J.H., Roberts, J.D., Macklin, W.B., Somogyi, P., and Bergles, D.E. (2005). Climbing fiber innervation of NG2-expressing glia in the mammalian cerebellum. *Neuron* 46, 773-785.

Lindvall, O., Ernfors, P., Bengzon, J., Kokaia, Z., Smith, M.L., Siesjo, B.K., and Persson, H. (1992). Differential regulation of mRNAs for nerve growth factor, brain-derived neurotrophic factor, and neurotrophin 3 in the adult rat brain following cerebral ischemia and hypoglycemic coma. *Proc. Natl. Acad. Sci. U S A.*

89, 648-652.

Linkenhoker, B.A., and Knudsen, E.I. (2002). Incremental training increases the plasticity of the auditory space map in adult barn owls. *Nature* 419, 293-296.

Linnarsson, S., Bjorklund, A., and Ernfors, P. (1997). Learning deficit in BDNF mutant mice. *Eur. J. Neurosci.* 9, 2581-2587.

Liu, M., Pleasure, S.J., Collins, A.E., Noebels, J.L., Naya, F.J., Tsai, M.J., and Lowenstein, D.H. (2000). Loss of BETA2/NeuroD leads to malformation of the dentate gyrus and epilepsy. *Proc. Natl. Acad. Sci. USA* 97, 865-870.

Liu, X., Wang, Q., Haydar, T.F., and Bordey, A. (2005). Nonsynaptic GABA signaling in postnatal subventricular zone controls proliferation of GFAP-expressing progenitors. *Nat. Neurosci.* 8, 1179-1187.

Lopez-Bendito, G., and Molnar, Z. (2003). Thalamocortical development: how we are going to get there. *Nat Rev. Neurosci.* 4:276-289.

LoTurco, J.J., Owens, D.F., Heath, M.J., Davis, M.B., and Kriegstein, A.R. (1995). GABA and glutamate depolarize cortical progenitor cells and inhibit DNA synthesis. *Neuron* 15, 1287-1298.

Ma, Y.L., Wang, H.L., Wu, H.C., Wei, C.L., and Lee, E.H. (1998). Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats. *Neurosci.* 82, 957-67.

Maffei, A., Nataraj, K., Nelson, S.B., and Turrigiano, G.G. (2006). Potentiation of cortical inhibition by visual deprivation. *Nature* 443, 81-84.

Malberg, J.E., Eisch, A.J., Nestler, E.J., and Duman, R.S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J. Neurosci.* 20, 9104-9110.

Malenka, R.C. and Nicol, R. (1999). Long-term potentiation-A decade of progress? *Science* 285, 1870-1874.

Mamounas, L.A., Blue, M.E., Siuciak, J.A., and Altar, C.A. (1995). Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *J. Neurosci.* 15, 7929-7939.

Markram, H., Toledo-Rodriguez, M., Wang, Y., Gupta, A., Silberberg, G., and Wu, C. (2004). Interneurons of the neocortical inhibitory system. *Nat. Rev. Neurosci.* 5, 793-807.

Marty, S., Wehrle, R., and Sotelo, C. (2000). Neuronal activity and brain-derived neurotrophic factor regulate the density of inhibitory synapses in organotypic

slice cultures of postnatal hippocampus. *J. Neurosci.* 20, 8087-8095.

Mathern, G.W., Babb, T.L., Pretorius, J.K., and Leite, J.P. (1995). Reactive synaptogenesis and neuron densities for neuropeptide Y, somatostatin, and glutamate decarboxylase immunoreactivity in the epileptogenic human fascia dentate. *J. Neurosci.* 15, 3990-4004.

Matsunura, N., Yoshida, N., Ohta, A., and Hisatsune, T. (2003). Neural precursor cells from adult mouse cerebral cortex differentiate into both neurons and oligodendrocytes. *Cytotechnol.* 43, 19-25.

Matsuyama, S., Nei, K., and Tanaka, C. (1997). Regulation of GABA release via NMDA and 5-HT1A receptors in guinea pig dentate gyrus. *Brain Res.* 761, 105-112.

McAllister, A.K., Lo, D.C., and Katz, L.C. (1995). Neurotrophins regulate dendritic growth in developing visual cortex. *Neuron* 15, 791-803.

McAllister, A.K., Katz, L.C., and Lo, D.C. (1997). Opposing roles for endogenous BDNF and NT-3 in regulating cortical dendritic growth *Neuron* 18, 767-778.

Meyer, A.H., Katona, I., Blatow, M., Rozov, A., and Monyer, H. (2002). In vivo labeling of parvalbumin-positive interneurons and analysis of electrical coupling in identified neurons. *J. Neurosci.* 22, 7055-7064.

Miklic, S., Juric, D.M., and Caman-Krzan, M. (2004). Differences in the regulation of BDNF and NGF synthesis in cultured neonatal rat astrocytes. *Int. J. Dev. Neurosci.* 22, 119-130.

Ming, G.L., Wong, S.T., Henley, J., Yuan, X.B., Song, H.J., Spitzer, N.C., and Poo, M.M. Adaptation in the chemotactic guidance of nerve growth cones. *Nature* 417, 411-418.

Miyata, T., Maeda, T., and Lee, J.E. (1999). NeuroD is required for differentiation of the granule cells in the cerebellum and hippocampus. *Genes Dev.* 13, 1647-1652.

Miyata, T., Kawaguchi, A., Okano, H., and Ogawa, M. (2001). Asymmetric inheritance of radial glial fibers by cortical neurons. *Neuron* 31, 727-741.

Mott, D.D., Turner, D.A., Okazaki, M.M., and Lewis, D.V. (1997). Interneurons of the dentate-hilus border of the rat dentate gyrus: morphological and electrophysiological heterogeneity. *J. Neurosci.* 17, 3990-4005.

Mu, J.S., Li, W.P., Yao, Z.B., and Zhou, X.F. (1999). Deprivation of endogenous brain-derived neurotrophic factor results in impairment of spatial learning and memory in adult rats. *Brain Res.* 835, 259-265.

Murer, M.G., Boissiere, F., Yan, Q., Hunot, S., Villares, J., Faucheux, B., Agid, Y.,

Hirsch, E., and Raisman-Vozari, R. (1999). An immunohistochemical study of the distribution of brain-derived neurotrophic factor in the adult human brain, with particular reference to Alzheimer's disease. *Neurosci.* 88, 1015-1032.

Murer, M.G., Yan, Q., and Raisman-Vozari, R. (2001). Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. *Prog. Neurobiol.* 63, 71-124.

Murphy, D.D., Cole, N.B., and Segal, M. (1998). Brain-derived neurotrophic factor mediates estradiol-induced dendritic spine formation in hippocampal neurons. *Proc. Natl. Acad. Sci. U S A.* 95, 11412-11417.

Murray, K.D., Gall, C.M., Jones, E.G., and Isackson, P.J. (1994). Differential regulation of brain-derived neurotrophic factor and type II calcium/calmodulin-dependent protein kinase messenger RNA expression in Alzheimer's disease. *Neurosci.* 60, 37-48.

Nacher, J., Rosell, D.R., Alonso-Llosa, G., and McEwen, B.S. (2001). NMDA receptor antagonist treatment induces a long-lasting increase in the number of proliferating cells, PSA-NCAM-immunoreactive granule neurons and radial glia in the adult rat dentate gyrus. *Eur. J. Neurosci.* 13, 512-520.

Nakagawa, E., Aimi, Y., Yasuhara, O., Tooyama, I., Shimada, M., McGeer, P.L.,

and Kimura, H. (2000). Enhancement of progenitor cell division in the dentate gyrus triggered by initial limbic seizures in rat models of epilepsy. *Epilepsia* 41, 10-18.

Narisawa-Saito, M., Wakabayashi, K., Tsuji, S., Takahashi, H., and Nawa, H. (1996). Regional specificity of alterations in NGF, BDNF and NT-3 levels in Alzheimer's disease. *Neuroreport* 7, 2925-2928.

Neher, E. and Sakmann, B. (1976). Single channel currents recorded from membrane of denervated frog muscle fibers. *Nature* 260, 799-802.

Nguyen, L., Rigo, J.M., Rocher, V., Belachew, S., Malgrange, B., Rogister, B., Leprince, P., and Moonen, G. (2001). Neurotransmitters as early signals for central nervous system development. *Cell Tissue Res.* 305, 187-202.

Nguyen, L., Malgrange, B., Breuskin, I., Bettendorff, L., Moonen, G., Belachew, S., and Rigo, J.M. (2003). Autocrine/paracrine activation of the GABA<sub>A</sub> receptor inhibits the proliferation of neurogenic polysialylated neural cell adhesion molecule (PSA-NCAM+) precursor cells from postnatal striatum. *J. Neurosci.* 23, 3278-3294.

Noctor, S.C., Flint, A.C., Weissman, T.A., Dammerman, R.S., and Kriegstein, A.R. (2001). Neurons derived from radial glial cells establish radial units in neocortex. *Nature* 409, 714-720.

Noctor, S.C., Flint, A.C., Weissman, T.A., Wong, W.S., Clinton, B.K., and Kriegstein, A.R. (2002). Dividing precursor cells of the embryonic cortical ventricular zone have morphological and molecular characteristics of radial glia. *J. Neurosci.* 22, 3161-3173.

Noctor, S.C., Martinez-Cerdeno, V., Ivic, L., and Kriegstein, A.R. (2004). Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. *Nat. Neurosci.* 7, 136-144.

Obenaus, A., Esclapez, M., and Houser, C.R. (1993). Loss of glutamate decarboxylase mRNA-containing neurons in the rat dentate gyrus following pilocarpine-induced seizures. *J. Neurosci.* 13, 4470-4485.

Obrietan, K., Gao, X.B., and van den Pol, A.N. (2002). Excitatory actions of GABA increase BDNF expression via a MAPK-CREB-dependent mechanism-a positive feedback circuit in developing neurons. *J. Neurophysiol.* 88, 1005-1015.

Okada. H., Miyakawa. N., Mori. H., Mishina. M., Miyamoto. Y., and Hisatsune. T. (2003). NMDA receptors in cortical development are essential for the generation of coordinated increases in [Ca<sup>2+</sup>]<sub>i</sub> in "neuronal domains". *Cereb. Cortex* 13, 749-757.

Overstreet-Wadiche, L.S., Bensen, A.L., and Westbrook, G.L. (2006). Delayed development of adult-generated granule cells in dentate gyrus. *J. Neurosci.* 26,

2326-2334.

Owens, D.F., and Kriegstein, A.R. (2002). Is there more to GABA than synaptic inhibition? *Nat. Rev. Neurosci.* 3, 715-727.

Palmer, T.D., Markakis, E.A., Willhoite, A.R., Safar, F., and Gage, F.H. (1999). Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. *J. Neurosci.* 19, 8487-8497.

Palmer, T.D., Willhoite, A.R., and Gage, F.H. (2000). Vascular niche for adult hippocampal neurogenesis. *J. Comp. Neurol.* 425, 479-494.

Parent, J.M., Yu, T.W., Leibowitz, R.T., Geschwind, D.H., Sloviter, R.S., and Lowenstein, D.H. (1997). Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J. Neurosci.* 17, 3727-3738.

Patterson, S.L., Grover, L.M., Schwartzkroin, P.A., and Bothwell, M. (1992). Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs. *Neuron* 9, 1081-1088.

Patterson, S.L., Pittenger, C., Morozov, A., Martin, K.C., Scanlin, H., Drake, C., and Kandel, E.R. (2001). Some forms of cAMP-mediated long-lasting potentiation are associated with release of BDNF and nuclear translocation of phospho-MAP kinase. *Neuron* 32, 123-140.

Paukert, M., and Bergles, D.E. (2006). Synaptic communication between neurons and NG2+

cells. *Curr. Opin. Neurobiol.* 16, 515-521.

Paxinos, G., and Franklin, K.B. (2001). The mouse brain in stereotaxic coordinates. 2<sup>nd</sup> Ed. Academic Press.

Phillips, H.S., Hains, J.M., Armanini, M., Laramee, G.R., Johnson, S.A., and Winslow, J.W. (1991). BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. *Neuron* 7, 695-702.

Radley, J.J., and Jacobs, B.L. (2003). Pilocarpine-induced status epilepticus increases cell proliferation in the dentate gyrus of adult rats via a 5-HT1A receptor-dependent mechanism. *Brain Res.* 966, 1-12.

Rakic, P. (1985). Limits of neurogenesis in primates. *Science* 227, 1054-1056.

Rakic, P. (1995). A small step for the cell, a giant leap for mankind: A hypothesis of neocortical expansion during evolution. *Trends. Neurosci.* 18, 383-388.

Rocamora, N., Welker, E., Pascual, M., and Soriano, E. (1996). Upregulation of BDNF mRNA expression in the barrel cortex of adult mice after sensory stimulation. *J. Neurosci.* 16, 4411-4419.

Rosenblum, K., Maroun, M., and Richter-Levin, G. (1999). Frequency-dependent inhibition in the dentate gyrus is attenuated by the NMDA receptor blocker

MK-801 at doses that do not yet affect long-term potentiation. Hippocampus 9, 491-494.

Rudolph, U. and Möhler, H. (2006). GABA-based therapeutic approaches: GABA<sub>A</sub> receptor subtype functions. Cur. Opin. Pharmacol. 6, 18-23.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., and Hen, R. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301, 805-809.

Saransaari, P., and Oja, S.S. (1999). Taurine release is enhanced in cell-damaging conditions in cultured cerebral cortical astrocytes. Neurochem. Res. 24, 1523-1529.

Schmidt-Hieber, C., Jonas, P., and Bischofberger, J. (2004). Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429, 184-187.

Scholzen, T., and Gerdes, J. (2000). The Ki-67 proteins: from the known and unknown. J. Cell. Physiol. 182, 311-322.

Schwab, M.H., Bartholomae, A., Heimrich, B., Feldmeyer, D., Druffel-Augustin, S., Goebbels, S., Naya, F.J., Zhao, S., Frotscher, M., Tsai, M.J., and Nave, K.A. (2000).

Neuronal basic helix-loop-helix proteins (NEX and BETA2/Neuro D) regulate terminal granule cell differentiation in the hippocampus. *J. Neurosci.* 20, 3714-3724.

Seki, T., and Arai, Y. (1991). The persistent expression of a highly polysialylated NCAM in the dentate gyrus of the adult rat. *Neurosci. Res.* 12, 503-513.

Seki, T., and Arai, Y. (1993). Highly polysialylated neural cell adhesion molecule (NCAM-H) is expressed by newly generated granule cells in the dentate gyrus of the adult rat. *J. Neurosci.* 13, 2351-2358.

Seki, T. (2002a). Expression patterns of immature neuronal markers PSA-NCAM, CRMP-4 and NeuroD in the hippocampus of young adult and aged rodents. *J. Neurosci. Res.* 70, 327-334.

Seki, T. (2002b). Hippocampal adult neurogenesis occurs in a microenvironment provided by PSA-NCAM-expressing immature neurons. *J. Neurosci. Res.* 69, 772-783.

Sendtner, M. (1996). Neurotrophic factors for experimental treatment of motoneuron disease. *Prog. Brain Res.* 109, 365-371.

Seri, B., Garcia-Verdugo, J.M., McEwen, B.S., and Alvarez-Buylla, A. (2001). Astrocyte give rise to new neurons in the adult mammalian hippocampus. *J.*

*Neurosci.* 21, 7153-7160.

Seri, B., Garcia-Verdugo, J.M., Collado-Morente, L., McEwen, B.S., and Alvarez-Buylla, A. (2004). Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. *J. Comp. Neurol.* 25, 359-378.

Shors, T.J., Mlesegaes, G., Beylin, A., Zhao, M., Rydel, T., and Gould, E. (2001). Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 410, 372-376.

Somogyi, P., and Klausberger, T. (2005). Defined types of cortical interneurone structure space and spike timing in the hippocampus. *J. Physiol.* 562, 9-26.

Spalding, K.L., Bhardwaj, R.D., Buchholz, B.A., Druid, H., and Frisen, J. (2005). Retrospective birth dating of cells in humans. *Cell* 122, 133-143.

Steiner, B., Kronenberg, G., Jessberger, S., Brandt, M.D., Reuter, K., and Kempermann, G. (2004). Differential regulation of gliogenesis in the context of adult hippocampal neurogenesis in mice. *Glia* 46, 41-52.

Sur, M., and Leamey, C.A. (2001). Development and plasticity of cortical areas and networks. *Nat Rev. Neurosci.* 2:251-262.

Tashiro, A., Sandler, V.M., Toni, N., Zhao, C., and Gage, F.H. (2006). NMDA-receptor-mediated, cell-specific integration of new neurons in adult

dentate gyrus. *Nature* 442, 929-933.

Tozuka, Y., Fukuda, S., Namba, T., Seki, T., and Hisatsune, T. (2005). GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells. *Neuron* 47, 803-815.

Tucker, K.L., Meyer, M., and Barde, Y.A. (2001). Neurotrophins are required for nerve growth during development. *Nat. Neurosci.* 4, 29-37.

van Praag, H., Schinder, A.F., Christie, B.R., Toni, N., Palmer, T.D., and Gage, F.H. (2002). Functional neurogenesis in the adult hippocampus. *Nature* 415, 1030-1034.

Vicario-Abejon, C., Collin, C., McKay, R.D., and Segal, M. (1998). Neurotrophins induce formation of functional excitatory and inhibitory synapses between cultured hippocampal neurons. *J. Neurosci.* 18, 7256-7271.

Vicario-Abejon, C., Owens, D., McKay, R., and Segal, M. (2002). Role of neurotrophins in central synapse formation and stabilization. *Nat Rev Neurosci.* 3, 965-974.

Wang, X., Merzenich, M.M., Sameshima, K., and Jenkins, W.M. (1995). Remodelling of hand representation in adult cortex determined by timing of tactile stimulation. *Nature* 378, 71-75.

Wang, D.D., Krueger, D.D., and Bordey, A. (2003). GABA depolarizes neuronal progenitors of the postnatal subventricular zone via GABAA receptor activation. *J. Physiol.* 550, 785-800.

Wang, L-P., Kempermann, G., and Kettenmann, H. (2005). A subpopulation of precursor cells in the mouse dentate gyrus receives synaptic GABAergic input. *Mol. Cell. Neurosci.* 29, 181-189.

Weissman, T.A., Riquelme, P.A., Ivic, L., Flint, A.C., and Kriegstein, A.R. (2004). Calcium waves propagate through radial glial cells and modulate proliferation in the developing neocortex. *Neuron* 43, 647-661.

Welker, E. Soriano, E., Dorfl, J., and Van der Loos, H. (1989). Plasticity of the barrel cortex of the adult mouse: transient increase of GAD-immunoreactivity following sensory stimulation. *Exp. Brain Res.* 78, 659-664.

West, M.J. (1999). Stereological methods for estimating the total number of neurons and synapses: issues of precision and bias. *Trends Neurosci.* 22, 51-61.

Wilson, I.A., Gallagher, M., Eichenbaum, H., and Tanila, H. (2006). Neurocognitive aging: prior memories hinder new hippocampal encoding. *Trends Neurosci.* 29, 662-670.

Yamaguchi, M., Saito, H., Suzuki, M., and Mori, K. (2000). Visualization of

neurogenesis in the central nervous system using nestin promoter-GFP transgenic mice. *Neuroreport* 11, 1991-1996.

Yang, Z., Suzuki, R., Daniels, S.B., Brunquell, C.B., Sala, C.J., and Nishiyama, A. (2006). NG2 glial cells provide a favorable substrate for growing axons. *J. Neurosci.* 26, 3829-3839.

Yoshida, M., Fukuda, S., Tozuka, Y., Miyamoto, Y., and Hisatsune, T. (2004). Developmental shift in bi-directional functions of taurine-sensitive chloride channels during circuit formation in postnatal mouse brain. *J. Neurobiol.* 60, 166-175.

Zafra, F., Lindholm, D., Castren, E., Hartikka, J., and Thoenen, H. (1992). Regulation of brain-derived neurotrophic factor and nerve growth factor mRNA in primary cultures of hippocampal neurons and astrocytes. *J. Neurosci.* 12, 4793-4799.

Zhang, X., and Poo, M.M. (2002). Localized synaptic potentiation by BDNF requires local protein synthesis in the developing axon. *Neuron* 36, 675-688.

松村直人 博士論文「成体の大脳皮質に存在するネスチング陽性細胞の分化特性に関する研究」(2004)

太田綾 修士論文「成体マウス大脳新皮質における神経系前駆細胞の *in vivo* での性質に関する研究」(2004)

相澤憲 修士論文「老齢カニクイザルにおける視覚弁別学習の能力減衰」(2006)

井出陽子 修士論文「成体海馬における新生ニューロンの成熟過程に関する研究」(2006)

田中裕一 修士論文「成体マウス大脳新皮質に存在するネストチン陽性細胞の性質およびニューロン分化能の解析」(2006)

高田徹夫 修士論文「GABA 刺激は成体大脳皮質 Nestin 陽性細胞からの BDNF 放出を促進する」(2007)

工藤佳久 細胞工学 解明が進むグリア細胞の役割 グリア・ニューロン回路網が支える脳機能 (秀潤社、2003)

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